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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,818	01/23/2006	Johannes Grosse	ING-122	6337

7590 05/12/2008

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EXAMINER	
HA, JULIE	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
05/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,818	GROSSE ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *208-371* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *208-371* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group 1, claim(s) 208-224, drawn to an isolated protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4.

Group 2, claim(s) 225-226, drawn to an isolated nucleic acid encoding a protein or a fragment of such protein, or an isolated nucleic acid which is complementary thereto.

Group 3, claim(s) 227-231, drawn to an episomal element comprising a nucleic acid.

Group 4, claim(s) 232-237, 321, drawn to an antisense nucleic acid and a pharmaceutical composition comprising a nucleotide sequence which is complementary to SEQ ID NO:3 or SEQ ID NO:4.

Group 5, claim(s) 238-244, 322, drawn to a short interfering RNA (siRNA) and a pharmaceutical composition comprising a double stranded nucleotide sequence wherein one strand is complementary to an at least 19, 20, 21, 22, 23, 24, or 25 nucleotide long segment of an mRNA encoding SEQ ID NO:3 or SEQ ID NO:4.

Group 6, claim(s) 245 and 323, drawn to an anticalin specifically binding an epitope in a protein which corresponds to SEQ ID NO:3 or SEQ ID NO:4 and a pharmaceutical composition comprising anticalin.

Group 7, claim(s) 246 and 324, drawn to an aptamer specifically binding an epitope in a protein which corresponds to SEQ ID NO:3 or SEQ ID NO:4 and a pharmaceutical composition.

Group 8, claim(s) 247-263, drawn to a non-human vertebrate animal comprising in the genome of at least some of its cells an allele of a gene encoding a protein having at

least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4.

Group 9, claim(s) 264-265, 267, 269, 271, 273-283, 286-304, 307-320, drawn to a method for the identification of a protein diagnostic marker for a goblet cell-related disorder.

Group 10, claim(s) 264-265, 267, 269, 271, 273-285, 288-306, 311-320, drawn to a method for the identification of a nucleic acid diagnostic marker for a goblet cell-related disorder.

Group 11, claim(s) 266, 268, 270, 272, drawn to a method for studying the molecular mechanisms of, or physiological processes associated with, conditions associated with, or affected by, reduced activity or undesirable activity of endogenous AGR2, reduced expression, reduced production or undesirable, or for the identification and testing of an agent useful in the prevention, amelioration, or treatment of these conditions.

Group 12, claim(s) 325-326, drawn to a method of producing a mutant AGR2 protein comprising culturing a host cell.

Group 13, claim(s) 327, 331, 334, 337, 340, 343, drawn to a method of gene therapy comprising delivering to cells in a human subject suffering from or known to be at risk of developing a condition associated with an alteration in goblet cell function a DNA construct comprising (a), (b) or (c).

Group 14, claim(s) 328, 332, 335, 338, 341, 344, drawn to a method of gene therapy comprising delivering to cells in a human subject a DNA construct comprising a DNA sequence encoding an siRNA.

Group 15, claim(s) 329, 333, 336, 339, 342, 345, drawn to a method of gene therapy comprising delivering to cells in a human subject a DNA construct comprising a DNA sequence encoding an aptamer.

Group 16, claim(s) 346-348, drawn to a method of preventing, treating, or ameliorating a medical condition in a human subject, the method comprising administering to said human subject a pharmaceutical composition comprising an agent capable of modulating AGR2 activity in said human subject, wherein said pharmaceutical composition is an antisense nucleic acid.

Group 17, claim(s) 346-347 and 349, drawn to a method of preventing, treating, or ameliorating a medical condition in a human subject, the method comprising administering to said human subject a pharmaceutical composition comprising an agent

capable of modulating AGR2 activity in said human subject, wherein said pharmaceutical composition is an siRNA.

Group 18, claim(s) 346-347, and 350, drawn to a method of preventing, treating, or ameliorating a medical condition in a human subject, the method comprising administering to said human subject a pharmaceutical composition comprising an agent capable of modulating AGR2 activity in said human subject, wherein said pharmaceutical composition is an anticalin.

Group 19, claim(s) 346-347 and 351, drawn to a method of preventing, treating, or ameliorating a medical condition in a human subject, the method comprising administering to said human subject a pharmaceutical composition comprising an agent capable of modulating AGR2 activity in said human subject, wherein said pharmaceutical composition is an aptamer.

Group 20, claim(s) 346-347 and 352, drawn to a method of preventing, treating, or ameliorating a medical condition in a human subject, the method comprising administering to said human subject a pharmaceutical composition comprising an agent capable of modulating AGR2 activity in said human subject, wherein said pharmaceutical composition is an isolated protein having the sequence of the human AGR2 protein according to SEQ ID NO:4.

Group 21, claim(s) 346-347 and 352, drawn to a method of preventing, treating, or ameliorating a medical condition in a human subject, the method comprising administering to said human subject a pharmaceutical composition comprising an agent capable of modulating AGR2 activity in said human subject, wherein said pharmaceutical composition is an isolated protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% amino acid identity to SEQ ID NO:3 or SEQ ID NO: 4.

Group 22, claim(s) 346-347 and 352, drawn to a method of preventing, treating, or ameliorating a medical condition in a human subject, the method comprising administering to said human subject a pharmaceutical composition comprising an agent capable of modulating AGR2 activity in said human subject, wherein said pharmaceutical composition is an isolated fragment of the protein corresponding to SEQ ID NO:3 or SEQ ID NO: 4.

Group 23, claim(s) 346-347 and 352, drawn to a method of preventing, treating, or ameliorating a medical condition in a human subject, the method comprising administering to said human subject a pharmaceutical composition comprising an agent capable of modulating AGR2 activity in said human subject, wherein said pharmaceutical composition is fusion protein comprising a protein or protein fragment corresponding to SEQ ID NO:3 or SEQ ID NO:4.

Group 24, claim(s) 346-347 and 352, drawn to a method of preventing, treating, or ameliorating a medical condition in a human subject, the method comprising administering to said human subject a pharmaceutical composition comprising an agent capable of modulating AGR2 activity in said human subject, wherein said pharmaceutical composition is an antibody specifically recognizing an epitope comprised within the human AGR2 protein according to SEQ ID NO:4.

Group 25, claim(s) 346-347 and 352, drawn to a method of preventing, treating, or ameliorating a medical condition in a human subject, the method comprising administering to said human subject a pharmaceutical composition comprising an agent capable of modulating AGR2 activity in said human subject, wherein said pharmaceutical composition is an antisense nucleic acid comprising a nucleotide sequence which is complementary to an mRNA encoding the human AGR2 protein according to SEQ ID NO:4.

Group 26, claim(s) 353-368, drawn to a method of identifying an agent useful in the prevention, amelioration or treatment of a goblet cell-related disorder, the method comprising a) culturing mammalian goblet cells in the presence or absence of a candidate agent and b) determining whether the presence of the agent results in a decrease in the production by the cells of mucus and/or one or more particular mucus constituents.

Group 27, claim(s) 369-371, drawn to an agent identified or identifiable by a method.

2. The inventions listed as Groups 1-27 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The isolated peptides having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% to SEQ ID NO:3 or SEQ ID NO:4 are patentably independent and distinct due to the different amino acid content of SEQ ID NOS:3 and 4 and due to the different sequence homology to SEQ ID NOS:3 and 4. For example SEQ ID NOS:3 and 4 both have 175 amino acid residues, and 65% sequence homology would require that at least 114 of the 175 amino acid must have sequence homology to SEQ ID NO: 3 or 4. That means that 61 residues can be different. Mathematical calculation implies that $61^{20} = 5.09X10^{35}$ different variations for the 61 amino acid. And since there are 175 amino acid total, the possibilities are vast. The core sequence has not been identified, thus there are no common structure. Thus, lack of unity is present in the instant application. The MPEP states the following:

The situation involving the so-called Markush practice wherein a single claim defines alternatives (chemical or non-chemical) is also governed by PCT Rule 13.2. In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in PCT Rule 13.2, shall be considered to be met when the alternatives are of a similar nature.

When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

(A) All alternatives have a common property or activity; and

(B)

(1) A common structure is present, i.e., a significant structural element is shared by all of the alternatives; or

(B)

(2) In cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

In paragraph (B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art, and the common structure is essential to the common property or activity. The structural element may be a single component or a combination of individual components linked together.

3. In paragraph (B)(2), above, the words "recognized class of chemical compounds" mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved.

4. Additionally, regarding the method claims the MPEP states the following: Unity of invention has to be considered in the first place only in relation to the independent claims in an international application and not the dependent claims. By "dependent" claim is meant a claim which contains all the features of one or more other claims and contains a reference, preferably at the beginning, to the other claim or claims and then states the additional features claimed (PCT Rule 6.4). The examiner should bear in mind that a claim may also contain a reference to another claim even if it is not a dependent claim as defined in PCT Rule 6.4. One example of this is a claim referring to a claim of a different category (for example, "Apparatus for carrying out the process of Claim 1 ...," or "Process for the manufacture of the product of Claim 1 ..."). Similarly, a claim to one part referring to another cooperating part, for example, "plug for cooperation with the socket of Claim 1 ...") is not a dependent claim (see MPEP 1850). Therefore, the method claims are in a different category: method of using the products. Therefore, these claims lack unity of invention.

Rejoinder

5. The examiner has required restriction between product and process claims.

Where applicant elects claims directed to the product, and the product claims are

subsequently found allowable, withdrawn process claims that depend from or otherwise

require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

6. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

7. **Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined** even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

8. The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

9. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

10. **Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.**

Election of Species

11. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

Different isolated protein or protein fragment (genera): due to different homology and different sequences;

Different isolated nucleic acid (genera) encoding a protein or a fragment: due to different protein sequences;

Different episomal element: due to different protein sequences;

Different antisense nucleic acid comprising a nucleotide sequence: due to different protein sequences;

Different short interfering RNA: due to different protein sequences;

Different anticalin biding to an epitope in a protein: due to different protein sequences;

Different aptamer binding an epitope in a protein: due to different protein sequences;

Different non-human vertebrate: Due to different family and class of animals that belong to the genus;

Different disease or disorders: asthma, chronic obstructive pulmonary disease COPD), cystic fibrosis, dry eye syndrome, gastric disease, peptic ulcer, inflammatory bowel disease, or intestinal cancer;

Different mucus constituent: mucin2 or trefoil peptide;

Different candidate agent: peptide or polypeptide (genus), a nucleic acid (genus) or small molecule (genus).

12. Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

13. For any group elected, Applicant is required to elect a single disclosed species of a protein sequence (that is a SEQ ID NO) for Groups drawn to protein; a nucleic acid sequence (i.e., a SEQ ID NO) for Groups drawn to a nucleic acid sequence encoding the protein; an anticalin binding specific to epitope of protein sequence, etc. For any Group indicating treatment or diagnosing of a disease or disorder is elected, Applicant is further required to elect a single disclosed species of disease or disorder. For example, Applicant elects Group 5 and elects glutamic acid buffer, sucrose for tonicifying agent, and methylparaben as preservative, and further elects pancreatic secretion.

14. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

15. The claims are deemed to correspond to the species listed above in the following manner:

Claims 208-371.

The following claim(s) are generic: None.

16. The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Different isolated protein or protein fragment (genera) are patentably independent and distinct due to different homology and different sequences. Further, search for one would not necessarily lead to the other. Different isolated nucleic acid (genera) encoding a protein or a fragment are patentably independent and distinct due to different protein sequences. Nucleic acid sequences that encode the protein sequence would depend on the codons, further increasing the structural variances. Further, search for one would not necessarily lead to the other. Different episomal element are patentably independent and distinct due to different protein sequences. Further, search for one would not necessarily lead to the other. Different antisense nucleic acid comprising a nucleotide sequence of protein are patentably independent and distinct due to different protein sequences. As described above, nucleic acids encode the proteins via codons, further increasing the structural variability. Further, search for one would not necessarily lead to the other. Different short interfering RNA are patentably independent and distinct due to different protein sequences, as described above. Further, search for one would not necessarily lead to the other. Different anticalin biding to an epitope in a protein are patentably independent and distinct due to different protein sequences. Further, search for one would not necessarily lead to the other. Different aptamer binding an epitope in a protein are patentably independent and distinct due to different protein sequences. Further, search for one would not necessarily lead to the other. Different non-human

vertebrates are patentably independent and distinct due to different family and class of animals that belong to the genus. Further, search for one would not necessarily lead to the other. Different disease or disorders are patentably independent and distinct due to different mechanisms and different cells involved in the disease or disorder. For example, asthma involves the lung and the airways to and from the lung, and patients suffering from asthma experience shortness of breath and chest tightening and coughing; dry eye syndrome involves the eye. Patients suffering from asthma may not have the dry eye syndrome and vice versa. Further, search for one would not necessarily lead to the other, leading to independent searches. Different mucus constituents are patentably independent and distinct due to different amino acid contents of mucin2 or trefoil peptide. Further, search for one would not necessarily lead to the other.

17. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

18. The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are

added after the election, applicant must indicate which of these claims are readable on the elected species.

19. **Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.**

20. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Conclusion

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. H./
Examiner, Art Unit 1654

/Anish Gupta/
Primary Examiner, Art Unit 1654